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| FOLEY HOAG, LLP PATENT GROUP, WORLD TRADE CENTER WEST 155 SEAPORT BLVD BOSTON, MA 02110 | | | EXAMINER SCHNIZER, RICHARD A | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/500,933

Applicant(s)

SHANGGUAN ET AL.

Examiner

Richard Schnizer, Ph. D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34, 36-69, 71-142, 144-151 and 153-168 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-34, 36-69, 71-142, 144-151 and 153-168 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

An amendment was received and entered on 8/6/08.

Claims 1-34, 36-69, 71-142, 144-151, and 153-168 remain pending and are under consideration.

Oath/Declaration

A new oath or declaration was submitted on 8/6/08 that overcomes the previous objection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-147, and 153-168 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopoulos et al (US Patent 4,235,871) in view of Kikuchi et al (US 4,687,661) and Meers et al (US Patent 6,120,797).

Papahadjopoulos taught a variety of liposomes comprising nucleic acids such as DNA or RNA. See column 3, lines 28-40; column 6, lines 31-43; column 8, lines 45-68 column 13, lines 59-67; and claims 16 and 17. The liposomes may consist of a fusogenic lipid such as dioleoylphosphatidylethanolamine (DOPE) or phosphatidylserine

(PS), and may also comprise a variety of other lipids including cholesterol, see paragraph bridging columns 3 and 4. PS is a fusogenic lipid.

Papahadjopoulos taught a method of making liposomes by combining lipids as discussed above and nucleic acids in an inert to form an emulsion, thereafter forming a gel, and finally converting the gel to a suspension of liposomes by addition of an aqueous medium. See entire document, especially e.g. claim 1, and column 4, line 45 to column 6, line 30.

Regarding claim 89, Papahadjopoulos taught addition of an aqueous solvent to the gel, rather than addition of the gel to an aqueous solvent, but this detail is considered to be a simple matter of design choice, and is therefore an obvious variant of the method of Papahadjopoulos.

Regarding claims 111-122 and 146, Papahadjopoulos is silent as to the total amount of lipid forming and fusogenic lipid expressed as a weight-percent of the gel, but the amounts of these lipids are considered to be result-effective variables that are obvious to optimize in order to modulate the characteristics of the resultant liposomes. See e.g. column 4, lines 53-58; and column 6, lines 11-18 and 28-34.

Regarding claims 124-135, Papahadjopoulos is silent as to the ratio of the weight of the increment of aqueous medium that can be used to wash the gel, and the weight of the gel itself. However, this is a parameter that would be routinely optimized by one of ordinary skill, see e.g. column 4, lines 53-58.

Regarding claims 136-140, Papahadjopoulos is silent as to the total amount of nucleic acid expressed as a weight-percent of the gel, but the amounts of the nucleic

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acid is clearly a result-effective variable that is routinely optimized by one of ordinary skill. in order to modulate the characteristics of the resultant liposomes. See e.g. column 6, lines 11-18 and 28-34.

Instant claim 145 requires that the gel or gel particles lack a hydrating agent, and that no hydrating agent is used in step A of the method. The specification defines a hydrating agent at paragraph 74 as a compound having at least two ionizable groups, one of which ionizable groups is capable of forming an easily dissociative ionic salt, which salt can complex with the ionic functionality of the liposome-forming lipid. Papahadjopoulos exemplifies the use of buffers comprising histidine and TES, both of which appear to meet the definition of a "hydrating agent". However, Papahadjopoulos did not require that the aqueous phase added to the lipids must be buffered, but only that it comprises the biological agent to be encapsulated. The inclusion or exclusion of a buffering agent in the aqueous phase is a matter of design choice, as is the selection of any particular buffering agent. It would have been obvious to one of ordinary skill in the art to either include in, or exclude from, the aqueous phase an ionizable agent such as a buffer. If one chose to include a buffer, it would have been obvious to use any known biological buffer, including monoionic buffers such as imidazole.

Regarding claim 146, Papahadjopoulos is silent as to the total amount of organic solvent remaining in the gel, but it is clear that this is a result-effective variable that is routinely optimized by one of ordinary skill. See e.g. column 4, lines 53-58.

Papahadjopoulos did not teach a water miscible organic solvent or N-acyl phosphatidylethanolamines.

Kikuchi taught that the use of volatile organic solvents for dissolution of lipids in methods of making liposomes was problematic because these organic solvents tend to remain in the final preparation and can be harmful to human health. Kikuchi suggests the use of water miscible organic solvents, such as ethylene glycol, for dissolution of lipids in methods of preparing liposomes. See column 1, line 60 to column 2, line 14; and column 2, lines 42-50.

Meers taught N-acyl phosphatidylethanolamines, including a N-dodecanoyl dioleoyl phosphatidylethanolamine, for use in liposome formation. See e.g. abstract; and column 4, lines 40-51.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the water miscible solvent of Kikuchi in the method of Papahadjopoulos because Kikuchi taught that the use of water miscible organic solvents was safer for applications in which the product liposomes were to be used in vivo. It would have been similarly obvious to use the lipid of Meers in the liposomes of Papahadjopoulos because Meers taught that it promotes membrane fusion. See e.g. column 1, lines 48-60.

Thus the invention as a whole was prima facie obvious.

Claims 17-24, 26-28, 32, 91-98, 100, 101, 105, and 148-151 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopoulos, Kikuchi, and Meers, as applied to claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104,

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106-142, 144-151, and 153-168 above, and further in view of Eppstein et al (US Patent 4897355) taken with the evidence of GenBank Accession No. M77788.

The teachings of Papahadjopoulos, Kikuchi, and Meers are summarized above and render obvious methods of making liposomes comprising nucleic acids and N-acyl phosphatidylethanolamine lipids by solubilizing liposome-forming lipids in a water miscible organic solvent.

These references did not specifically teach plasmid DNA or oligonucleotides or the use of DOPE or DOPC.

Eppstein taught that liposomes could be used to encapsulate and deliver to cells plasmid DNAs and oligonucleotides, including pSVCAT (5 kbp) and oligonucleotides of an average length of about 130 bp. See column 3, lines 56-59; column 8, lines 32-40 and 43-45; column 10, lines 56-59; column 48 lines 24-50, and paragraph bridging columns 48 and 49. GenBank Accession No. M77788 provides evidence that PSVCAT is 5003 base pairs in length.

Eppstein also taught a variety of lipids that could be used to form liposomes including dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine, and cholesterol (see paragraph bridging columns 7 and 8; column 16, lines 53-and 54; and column 38, line 37).

Eppstein also taught methods of transfecting eukaryotic cells in vitro at 37°C (column 45, lines 43-52), as well as intravenous delivery to humans (see column 8, lines 1-13; column 10, lines 37-62; column 12, lines 48-53; column 13, lines 27-29; and column 20, lines 21-41).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method of Papahadjopoulos as modified by Kikuchi and Meers to encapsulate the plasmid or oligonucleotides of Eppstein because Papahadjopoulos suggests that the liposomes will protect nucleic acids from degradation (see e.g. column 13, lines 59-67), and because one of ordinary skill would clearly appreciate their utility for this purpose in view of the teachings of Eppstein. It would have been similarly obvious to use the lipids of Eppstein in the methods of Papahadjopoulos, because MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. In this case the lipids of Eppstein are clearly suitable for making liposomes. Finally it would have been obvious to use the liposomes to transfect eukaryotic cells in vitro or in vivo, as well as for intravenous delivery in humans because this was suggested by Eppstein.

Claims 82-86 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopoulos, Kikuchi, and Meers, as applied to claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-147, and 153-168 above, and further in view of Lenk et al (US Patent 5,169,637).

The teachings of Papahadjopoulos, Kikuchi, and Meers are summarized above and render obvious methods of making liposomes comprising nucleic acids and N-acyl phosphatidylethanolamine lipids by solubilizing liposome-forming lipids in a water miscible organic solvent.

The combined references did not specifically teach acetone, ethanol, methanol,

or 2-propanol as water-miscible organic solvents.

Lenk taught a variety of solvents that could be used to solubilize lipids, including acetone, ethanol, methanol, or 2-propanol. See table VI at column 40.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use in the invention of Papahadjopoulos any water miscible organic solvent that can be used to solubilize liposome-forming lipids in view of the teachings of Kikuchi, as discussed above. It would have been obvious to use acetone, ethanol, methanol, or 2-propanol because Lenk taught that these can be used to solubilize lipids. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Response to Arguments

Applicant's arguments filed 8/6/08 have been fully considered but they are not persuasive.

Applicant argues at pages 21-25 of the response that one of ordinary skill would not have substituted a water miscible solvent of Kikuchi for the water immiscible solvent of Papahadjopoulos because Papahadjopoulos taught that the water immiscible solvent was required for encapsulation (relying for support on column 3, lines 48-53 and column

6, lines 56-61). Applicant also asserts that Papahadjopoulos indicates that use of water-miscible organic solvents would render the invention inoperative and teaches away from such an embodiment (relying for support on column 6 lines 56-61). This is unpersuasive. The cited passages indicate that water-immiscible organic solvents are essential for "high capture", but do not provide any support for the position that the disclosed method would be non-functional if a water miscible solvent was substituted for the water immiscible solvent. Furthermore, Applicant has ignored the teachings of Kikuchi, who found that homogeneous liposomes can be obtained with ease and good reproducibility when membrane components forming liposomes are dissolved or swollen in a water-soluble and physiologically acceptable non-volatile organic solvent and the resulting mixture is further mixed and stirred with an aqueous medium. See column 1, line 62 to column 2, line 2. There is no evidence of record that use of a water miscible solvent in the method of Papahadjopoulos would render the method inoperative. Based on the teachings of Papahadjopoulos cited by Applicant, one might expect to see a decrease in encapsulation yield, but this is not evidence of inoperability. Further, in performing the substitution, one would gain the advantage of eliminating from the final product organic solvents that are harmful to human health, as taught by Kikuchi. Accordingly, there is a rational basis for substituting the water miscible solvent for the water immiscible solvent. It would have been obvious to one of ordinary skill to trade off a decrease in encapsulation efficiency for an increase in safety, and a possible increase in the maximum safe dose that could offset any encapsulation deficiency. For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer, Ph. D./
Primary Examiner, Art Unit 1635